REMARKS

Claims 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52 and 54-59 presently appear in this case. Claims 27-28 and 43-48 are currently withdrawn from consideration. No claims have been allowed. The official action of October 24, 2008, has now been carefully studied. Reconsideration and allowance are respectfully urged.

Briefly, the present invention relates to the administration of a glycosphingolipid cell activator of specified formula to a mammal in order to activate NKT cells, accelerate IL-4 production, accelerate IFN-γ production, activate dendritic cells, accelerating IL-12 production, accelerate IL-10 production, activate NK cells, inhibit herpesvirus activity, accelerate IL-6 production, and/or accelerate nitrogen monoxide production.

Claims 49, 53, and 54 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The examiner states that claim 49 lacks antecedent basis for "cell" and that the abbreviation "NO" makes claims 53 and 54 indefinite.

Claims 49 and 53 have been cancelled and claim 54 has been amended to define "NO" as "nitrogen monoxide," as is supported on page 34, line 7, of the specification. "Nitrogen monoxide" is synonymous with "nitric oxide." Accordingly, this rejection has now been obviated.

Claims 29-42 and 49-56 have been rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. The examiner states that the specification, while being enabling for a method of treating NKT cells, NK cells and dendritic cells, accelerating the production of cytokines, accelerating nitric oxide production, and inhibiting viral activity in cytomegalovirus (such as herpes virus) by administering particular glycolipids of formula (1), does not reasonably provide enablement for activating NKT cells, NK cells and dendritic cells, accelerating the production of cytokines, and inhibiting viral activity in any viral infection by administering any compound of formula (1). The examiner further states that the specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection is respectfully traversed.

First, as to the virus being treated, the present claims 50, 55 and 56 have now been amended to specify that the virus is herpesvirus, thus obviating this part of the rejection. The examiner has conceded that the disclosure is enabling for the treatment of herpesvirus by particular glycolipids of formula (1).

As to the scope of the definition of the glycolipids that can be used for the purpose of the present invention, the working examples in the present specification are indeed exemplary of all of the different kinds of structure covered by the claims. The differences among all of the specified structures for R^5 are relatively small from one to the other. They all have two long-chain alkyl groups attached to the same moiety. The differences that may include a cyclopropyl group on one of the long chain alkyl groups or a double bond between two carbon atoms in the long alkyl groups or the presence or absence of one hydroxy group would not be expected to substantially change the properties of the claimed compounds. The main differences are in the R^6 group, which can be hydrogen or one of several different sugars. However, each of these different types of structures are represented in the compounds tested. In GLS-1, representing Structure A, the R^6 is H. In GSL-2, representing Structure B, the R^6 is R^{62}. In GSL-3, representing Structure C, the R^6 is R^{63}. In GSL-4, representing Structure D, the R^6 is R^{64}. And in GSL-5, representing Structure E, the R^6 is R^{65}. Thus, all of the different types of structure are represented in the representative compounds of the examples.

In every single example (with one exception) the results of the tested compound was better than control. Thus,

there is insufficient reason to doubt the data in the extensive working examples as fairly representing the full breadth of the claimed compounds used in each of the methods. This is not the case of a hunting license. Applicant contends and each and every one of the voluminous working examples supports the contention that all of the compounds within the scope of the claims, all of which have substantially related structures, will be operable for each of the claimed methods. No selection (or hunting) is necessary.

The examiner's comments about some of the compounds having long alkyl or alkenyl chains is not relevant as all of the compounds have substantially equally long alkyl or alkenyl chains. Similarly, the examiner's comments about variability of stereocenters in treating viral infections is belied by the results of Example 9 in Table 10. Every one of the GSL's tested were much better than control, including GSL-6 and GSL-7 having different chirality.

The examiner's attention is invited to the statement of the CCPA in *In re Marzocchi*, 169 USPQ 367, 369-370 (CCPA 1971), where it states:

> In the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a broad statement put forward as enabling support for a claim; this will especially be the case where the statement is, on its

> face, contrary to generally accepted scientific principles; ... it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement; otherwise, there would be no need for the applicant to support his presumptively accurate disclosure.

See also MPEP 2107.02, which cites *Marzocchi* and confirms that statements of how to make and use the invention in the specification must be presumed accurate. Here, the examiner has not sufficiently explained, backed up by evidence, why applicant's presumptively accurate statements would be deemed incredible by one of ordinary skill in the art.

Additionally, it should be noted that claims 32, 34 and 36 have been amended to recite only R51-R53 and R62 to R65. At least these claims should be considered to be fully supported by an enabling disclosure in light of the more limited scope of the compounds.

For all of these reasons, all of the present claims, particularly as presently amended, fully comply with the enablement requirement of 35 USC 112. Reconsideration and withdrawal of the rejection are therefore respectfully urged.

Claims 29-34, 39-42, 49-52, 55 and 56 were rejected under 35 U.S.C. 103(3) as being unpatentable over Kakimi and

in view of Wu and Wiese. The examiner states that Kakimi teaches NKT cell activation by α-galactoceramide (α-GalCer) inhibits hepatitis B virus replication *in vivo*. The examiner states that Kakimi concludes that α-GlyCer inhibits HBV replication by directly activating NKT cells and by secondarily activating NK cells to secrete antiviral cytokines in the liver. The examiner states that Wu teaches bacterial glycolipids and analogs as antigens for CD1d-restricted NKT cells.

With respect to claims 30, 32 and 34, these claims have now been amended so as to be fully supported by the priority application. Submitted herewith is a translation of the priority application. Wu's reference was published on February 1, 2005, which is after the priority date of the present application (February 19, 2004). As indicated in the translation, the inventors disclose the subject matters of claims 30, 32 and 34 on the priority date. As Wu is not available as a reference against claims 30, 32 and 34, this rejection is no longer applicable. Reconsideration and withdrawal thereof insofar as it is applicable to claims 30, 32 and 34 are therefore respectfully urged.

The subject mater in claims 36, 38, 40, 42, 50, 52 and 54-56 are not made obvious by Kitami, Kitamura, Tay, Wu or Wiese. Kitami and Kitamura employ α-GalCer. The

glycolsphingolipid represented by formula (3) (hereinafter, referred to as GSL) has significant differences in the sugar head group and the ceramide portion from α-GalCer. Note that the Abstract of Wu concurs with this statement. In addition, Wu explicitly discloses that GSL has IFN-γ production activity and IL-4 production activity much smaller than those of α-GalCer (see page 1354, Fig. 6A of Wu). Accordingly, there would be no motivation to select GSL, having lesser activities, in order to achieve the invention recited in Claims 36, 38, 40, 42, 50, and 54-56.

Secondly, Wiese discloses that GSL acts as an activator of complement. The activity is distinctly different in mechanism from the activity recited in claims 36, 38, 40, 42, 50, 52 and 54-56. In Wu, GSL does not directly affect a cell, and only indirectly acts on the cell. In the present invention, GSL directly affects the cell, thereby enhancing the activities specified in claims 36, 38, 40, 42, 50, 52 and 54-56. Applicant believes that, if it were known that GSL had complement activation activity, a skilled person could still not have predicted that GSL has the activities recited in claims 36, 38, 40, 42, 50, 52 and 54-56.

Even if a certain chemical compound has an immunopharmacological activity, it is difficult to find out that the chemical compound has other specific

immunopharmacological activities. This fact is supported by the attached document, Homma et al, "Studies on Lipid A, the Active Center of Endotoxin – Structure-Activity Relationship," *Correlates in Pharmacostructures*, 14:645-655 (1989). Author Kumazawa is one of the inventors in the present application.

As shown at page 655, Table IV of the Homma et al., GLA-58 and GLA-69 have IFN activity and the IL-1 activity. On the other hand, as shown at page 658, Fig 16, GLA-58 and GLA-69 hardly have any antiviral activity. The data suggests that an IFN activity, an IL-1 activity and an antiviral activity may have less relationship to each other, particularly when a certain chemical compound does not necessarily have an antiviral activity. Similarly, GLA-62 has IL-1 activity, but it does not have TNF activity. As described above, immunopharmacological activities do not necessarily have relationship to one another. Homma et al. also supports this statement at page 661, right column. In order to find that a certain chemical compound has a certain immunopharmacological activity, the skilled person has to carry out quite a lot of experiments. Therefore, even though GSL has an IFN production activity, it would not have been reasonably predictable to the skilled person that GSL has the other claimed activities.

It is submitted that all of the claims now present in the case clearly define over the references of record and

fully comply with 35 USC §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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